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OFFICE OF POLLUTION PREVENTION AND TOXICS
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UNION CARBIDE CORPORATION 39 OLD RIDGEBURY ROAD, DANBURY, CT 06817-0001

8EHQ-0194-12870

January 14, 1994

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CERTIFIED MAIL
RETURN RECEIPT
REQUESTED

Document Processing Center (TS-790)
Office of Pollution Prevention & Toxics
U.S. Environmental Protection Agency
401 M Street., SW
Washington, DC 20460

Attn: 8(e) Coordinator

Dear Sir or Madam:

Union Carbide Corporation ("Union Carbide") herewith supplies the following information on isopropanol (CASRN 67-63-0) which the Agency might regard as being reportable under its current TSCA § 8(e) guidelines. This information concerns preliminary results from a 2-year rat inhalation study being conducted under a TSCA § 4 test rule, and is submitted to the Agency for its information. Union Carbide does not regard this as "substantial risk" information.

Isopropanol has been subject to testing for potential adverse health effects under provisions of a TSCA section 4 test rule. As part of the testing program, rats were exposed to isopropanol vapor for a period of 2 years. In that study, groups of 65 Fischer 344 rats of each sex were exposed to air concentrations of either 0, 500, 2500 or 5000 ppm for 6 hours a day, 5 days a week for at least 104 weeks. Surviving animals were sacrificed at the end of the exposure period and examinations were performed to evaluate effects of exposure. Ten additional animals, satellite groups, were exposed with the main group animals and sacrificed after 73 weeks of exposure. Examinations were also performed at this interim time interval to evaluate effects of exposure. Preliminary data from the study have been evaluated and presented in a draft report. The major findings in this draft report are summarized below:

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7 pgs.

- An increase in mortality rate in male rats exposed to the highest concentration (100% mortality by week 100 compared to 82% mortality in the control group at the end of the study).

- Clinical signs of toxicity noted in both sexes exposed at the two highest concentrations (i.e. hypoactivity, lack of startle reflex and narcosis during exposure at 5000 ppm).

- Increased body weight and body weight gain predominantly seen at the two highest concentrations in both male and female animals.

- Increased absolute and relative liver and kidney weights in males exposed to 5000 ppm (interim sacrifice at 73 weeks of exposure) and 2500 ppm and in females exposed to 5000 ppm isopropanol.

- Increased testes weights in males of the high exposure group at the interim sacrifice.

- An exposure related exacerbation of preexisting nephropathy particularly evident in males and females of the two higher exposure concentration groups.

- An increased incidence of a number of non-neoplastic lesions believed to be secondary or tertiary to the renal lesions.

- Evidence of chronic irritation to the tissues lining the nasal cavities of males and females exposed to 5000 ppm isopropanol.

- An exposure concentration related increase in the incidence of testicular seminiferous tubule atrophy and interstitial cell adenomas.

The incidence of interstitial cell tumors of the testes for all males (those examined from the interim sacrifice, those which died or were killed moribund and those which were examined after the final sacrifice) was 65, 85, 91 and 95 percent for the 0, 500, 2500 and 5000 ppm groups, respectively. The incidence of this neoplastic lesion in Fischer 344 rats is normally quite high. Historical control background incidence at the Bushy Run Research Laboratories range from 86 to 91 percent, and the reported range for this lesion is 64 to 98 percent [Haseman, J. K. and J. Arnold (1990) *Pathology of the Fischer Rat*, p555-564.] Thus, this result might arise from an unusually low incidence of the lesion in the concurrent control group of animals.

A copy of the draft abstract is attached.

A copy of the final report related to these observations will be sent to the Agency as part of the TSCA § 4 test rule agreement.

Please contact the undersigned with questions, if any, at 203/794-5230

Very truly yours,

William C. Kuryla, Ph.D.
Associate Director
Product Safety

WCK/jfh
Attachment

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01/14/94

DRAFT

BUSHY RUN RESEARCH CENTER
6702 Mellon Road, Export, Pennsylvania 15632-8902
Telephone (412) 733-5200
Telecopier (412) 733-4804

STUDY TITLE

Isopropanol Vapor Inhalation Oncogenicity Study in F-344 Rats

TEST SUBSTANCE

Isopropyl Alcohol

DATA REQUIREMENT

Isopropanol Final Test Rule, Section 4 of the Toxic Substances Control Act (TSCA), 40 CFR Part 795 and 799

AUTHORS

H. D. Burleigh-Flayer and C. L. Benson

DRAFT SUBMISSION DATE

December 21, 1993

PERFORMING LABORATORY

Bushy Run Research Center (BRRC)
Union Carbide Chemicals and
Plastics Company Inc. (UCC&P)
6702 Mellon Road
Export, PA 15632-8902

LABORATORY PROJECT ID

91N0133

SPONSOR

Isopropanol Panel
Chemical Manufacturers Association
2501 M Street, NW
Washington, DC 20037

Isopropanol Vapor Inhalation Oncogenicity Study in F-344 Rats

SUMMARY

Four groups of animals, each consisting of 75 F-344 rats/sex, were exposed to isopropanol vapor (CAS No. 67-63-0) at target concentrations of 0 (filtered air control), 500, 2500, or 5000 ppm. Animals were exposed for 6 hours/day, 5 consecutive days/week, for at least 104 weeks. Ten rats/sex/group were assigned to an interim sacrifice group and were sacrificed during Week 73. Monitors for toxic effects included clinical observations, body and organ weights, hematologic evaluations, necropsy observations, and microscopic evaluations.

Mean (± SD) isopropanol analytical concentrations of 504 (± 14), 2509 (± 58), and 5037 (± 115) ppm were measured. The mortality rates for male rats (including those sacrificed moribund but excluding interim sacrifice) from the 0, 500, 2500, and 5000 ppm groups were 82, 83, 91, and 100%, respectively. The last male rat from the 5000 ppm group died during Week 100. The corresponding values for female rats were 54, 48, 55, and 69%, respectively. The only difference ($p < 0.01$) in mean survival time was noted for the 5000 ppm group of male rats.

Clinical signs for some male and female rats were observed during exposures to 5000 ppm and included hypoactivity, lack of a startle reflex, and narcosis. Hypoactivity was also noted for some male and female rats during exposure to 2500 ppm. Clinical signs noted during nonexposure periods for male rats from the 5000 ppm group included emaciation, dehydration, and urine stains; clinical signs observed during nonexposure periods for female rats included swollen periocular tissue (5000 ppm group only) and urine stains (2500 and 5000 ppm groups). Decreased body weight and/or body weight gain were noted for male and female rats from the 5000 ppm group at the end of the first and second weeks of exposure. Following this timepoint, increased body weight and body weight gain were noted. For male rats from the 2500 and 5000 ppm groups, increased body weight and body weight gain were observed throughout the duration of the study. For female rats, concentration-related increases in body weight and body weight gain were observed throughout most of the study, although the increases observed for the 500 ppm group were slight and probably not biologically significant.

No exposure-related changes in hematologic parameters were observed for male or female rats from any isopropanol exposure group at any time period. At Weeks 57 and 58, urine chemistry for male and female rats from the 5000 ppm group revealed a decrease in glucose, a decrease in osmolality, and an increase in total protein (males only). Similarly, at Week 74 and at Week 108 (only female rats from the 5000 ppm group were surviving at this timepoint), a decrease in glucose and osmolality as well as increases in total protein and/or total volume were noted for male and female rats from the 5000 ppm group. Similar changes were observed for male rats from the 2500 ppm group at Week 74 and Week 104.

Absolute and/or relative (as a percentage of body and brain weight) liver and kidney weight were increased for male rats from the 5000 ppm group at the interim sacrifice and for male rats from the 2500 ppm group at the terminal

sacrifice. Relative liver weight (as a percentage of brain weight) was also increased for male rats from the 2500 ppm group at the interim sacrifice. For female rats from the 5000 ppm group at Week 109, an increase in absolute and relative (as a percentage of body and brain weight) liver and kidney weight was noted. Other organ weight changes included a concentration-related increase in testes weight (absolute and relative as a percentage of body and brain weight) observed for male rats at the interim sacrifice timepoint. An increase in absolute and relative (as a percentage of body and brain weight) lung weight was noted for female rats at Study Week 73, but not at Study Week 109.

At the interim sacrifice (Week 73), the only gross lesion noted was an exposure-related increase in granular kidneys for male rats from the 2500 and 5000 ppm groups. At the terminal sacrifice at Week 105, an increase in granular kidneys was observed again for male rats from the 2500 ppm group. For male rats which died or were sacrificed due to morbidity, an increased incidence of thickened stomachs, granular kidneys, and color change of the kidney was noted at necropsy for animals from the 2500 and 5000 ppm groups. No exposure-related gross lesions were observed for female rats from any of the isopropanol exposure groups at the interim or the terminal sacrifice. For female rats which died or were sacrificed due to morbidity, an increased incidence of thickened stomachs for animals from the 5000 ppm group and granular kidneys was noted for animals from the 2500 and 5000 ppm groups.

Microscopic evaluation revealed that the kidney was a target for nonneoplastic effects in rats exposed repeatedly to isopropanol vapor. Increased frequencies of a number of microscopic lesions were observed in the kidneys of male rats from the 2500 and 5000 ppm groups which died or were sacrificed moribund during the study and included mineralization, tubular dilation, glomerulosclerosis, interstitial nephritis, interstitial fibrosis, hydronephrosis, and transitional cell hyperplasia. In addition, an increase in the severity of many of these lesions was observed for male and female rats from the 2500 and 5000 ppm groups. An increased severity of glomerulosclerosis was observed for female rats from the 5000 ppm group at the terminal sacrifice (Week 109). An increase in the frequency of mineralization in a number of organs was also noted for male and female rats from the 2500 and 5000 ppm groups; this lesion was believed to be secondary to the renal lesions. Increased frequencies of other lesions which were believed to be a result of the renal lesions or increased soft tissue mineralization included cellular hyperplasia of the parathyroid glands (females only), myocardial degeneration/fibrosis, glandular ectasia within the gastric mucosa (females only), and fibrous osteodystrophy in male and female rats from the 5000 ppm group which died or were sacrificed due to morbidity.

Other nonneoplastic lesions which were observed with increased frequencies for male rats from the 5000 ppm group which died or were sacrificed due to morbidity included basophilic cell foci within the liver, splenic hemosiderosis, and rhinitis and squamous metaplasia of the respiratory epithelium within the nasal cavity. Other nonneoplastic lesions observed with increased frequencies for female rats from the 5000 ppm group which died or were sacrificed due to morbidity included atrial thrombosis, splenic hemosiderosis, ocular keratitis, rhinitis, dacryosolenitis (inflammation of the nasolacrimal duct), and squamous metaplasia of the respiratory epithelium within the nasal cavity.

The only neoplastic lesion observed during the study was interstitial cell adenomas of the testis. An increased frequency of testicular seminiferous tubule atrophy and interstitial cell adenomas of the testis was observed for male rats from the 5000 ppm group at the interim sacrifice. A concentration-related increase in interstitial cell adenomas of the testis was also noted for male rats which were found dead or sacrificed moribund during the study. For male rats found dead or sacrificed moribund, the frequencies of interstitial cell adenomas of the testis were 57.75, 80.9, 90.6, and 93.8% for the 0, 500, 2500, and 5000 ppm groups, respectively. The frequencies of this lesion for all male rats examined were 64.9, 84.6, 91.3, and 94.7% for the 0, 500, 2500, and 5000 ppm groups, respectively. A decrease in pituitary adenomas and granular lymphocyte leukemia was observed for male rats from the 5000 ppm group which died or were sacrificed due to morbidity; however, this was believed to be a result of their early mortality. There were no increased frequencies of neoplastic lesions for female rats. An exposure-related decrease in large granular lymphocyte leukemia was observed, however.

The main cause of death for male rats from the 5000 ppm group was chronic renal disease and was also considered to account for much of the mortality observed for the 2500 ppm group. The main cause of death for the male control rats was large granular lymphocyte leukemia. For female rats from the 5000 ppm group which died or were sacrificed due to morbidity, the main cause of death was chronic renal disease. The main cause of death for the female control rats was large granular lymphocyte leukemia.

In conclusion, exposure of rats to isopropanol vapor for 24 months produced clinical signs of toxicity (hypoactivity, lack of a startle reflex, or narcosis) during the exposures at 2500 and 5000 ppm as well as increases in body weight and body weight gain. Urine chemistry changes indicative of kidney damage were noted for male rats from the 2500 and 5000 ppm groups and female rats from the 5000 ppm group. A number of nonneoplastic lesions were observed, with the most significant lesions being observed in the kidney. The only neoplastic lesion observed for male rats was an increase in interstitial cell adenomas of the testis which was considered to represent marked hyperplasia and was not believed to represent autonomous growth. In addition, the increased incidences of testicular tumors in the isopropanol groups appear to be reflective of the lower incidence in the control group. No increased frequencies of neoplastic lesions were noted for female rats from any isopropanol exposure group. Thus, the no-observed-effect level (NOEL) for toxic effects was 500 ppm for both male and female rats. The NOEL for oncogenicity effects for both male and female rats was determined to be greater than 5000 ppm.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

William C. Kuryla, Ph.D.
Associate Director, Product Safety
Union Carbide Corporation
39 Old Ridgebury Road
Danbury, Connecticut 06817-0001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 1 2 1994

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000 Initial) assigned by EPA to your submission(s). Please cite this number when submitting follow-up or supplemental information and refer to the enclosure on the reverse side "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure

12870 A

OPPTS DATA
Submission # 8EHQ-994-12870 SEQ A

TYPE: INIT SUPP FLWP

SUBMITTER NAME: Union Carbide Corporation

INFORMATION REQUESTED FLWP DATE

0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
0678 CAP NOTICE

VOLUNTARY ACTIONS
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/ON-GOING
0403 NOTIFICATION OF NEW USES
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB DATE: 01/14/94 OTS DATE: 01/26/94 CSB DATE: 02/18/94

CHEMICAL NAME: CAS#

61-63-0

INFORMATION TYPE:		P	F	C
0201	ONCO (HUMAN)	01	02	04
(0202)	ONCO (ANIMAL)	(01)	02	04
0203	CELL TRANS (IN VITRO)	01	02	04
0204	MUTA (IN VITRO)	01	02	04
0205	MUTA (IN VIVO)	01	02	04
0206	REPRO/TERATO (HUMAN)	01	02	04
(0207)	REPRO/TERATO (ANIMAL)	(01)	02	04
0208	NEURO (HUMAN)	01	02	04
(0209)	NEURO (ANIMAL)	(01)	02	04
0210	ACUTE TOX. (HUMAN)	01	02	04
0211	CHR TOX. (HUMAN)	01	02	04
0212	ACUTE TOX. (ANIMAL)	01	02	04
0213	SUB ACUTE TOX (ANIMAL)	01	02	04
0214	SUB CHRONIC TOX (ANIMAL)	01	02	04
(0215)	CHRONIC TOX (ANIMAL)	(01)	02	04

INFORMATION TYPE:		P	F	C
0216	EPI/CLIN	01	02	04
0217	HUMAN EXPOS (PROD CONTAM)	01	02	04
0218	HUMAN EXPOS (ACCIDENTAL)	01	02	04
0219	HUMAN EXPOS (MONITORING)	01	02	04
0220	ECO/AQUA TOX	01	02	04
0221	ENV. OCCC/REL/FATE	01	02	04
0222	EMER INCI OF ENV CONTAM	01	02	04
0223	RESPONSE REQEST DELAY	01	02	04
0224	PROD/COMP/CHEM ID	01	02	04
0225	REPORTING RATIONALE	01	02	04
0226	CONFIDENTIAL	01	02	04
0227	ALLERG (HUMAN)	01	02	04
0228	ALLERG (ANIMAL)	01	02	04
0239	METAB/PHARMACO (ANIMAL)	01	02	04
0240	METAB/PHARMACO (HUMAN)	01	02	04

INFORMATION TYPE:	
0241	IMMUNO (ANIMAL)
0242	IMMUNO (HUMAN)
0243	CHEM/PHYS PROP
0244	CLASTO (IN VITRO)
0245	CLASTO (ANIMAL)
0246	CLASTO (HUMAN)
0247	DNA DAM/REPAIR
0248	PROD/USE/PROC
0251	MSDS
0299	OTHER

TRIAGE DATA:

NON-CBI INVENTORY: (YES) NO DETERMINE

ONGOING REVIEW: YES NO REVIEW

SPECIES: RAT

TOXICOLOGICAL CONCERN: LOW MED HIGH

USE:

PRODUCTION:

COMMENTS: Non-CAP

12870A Isopropanol

ONCO CONCERN: LOW

Oncogenicity

Exposure of Fischer 344 rats for 2 years by inhalation at concentrations of 500, 2500, or 5000 ppm (6 hours/day, 5 days/week) caused an increase in interstitial call adenomas of the testis. The incidence in dosed groups at increaseing concentrations was 85%, 91%, and 95% compared to 65% for controls. The range for this lesion in historical controls (NTP) is 64 to 98%. Therefore, the increase is possibly related to a lower than normal incidence in controls.

Chronic toxicity

Clinical signs of neurotoxicity (hypoactivity, lack of startle reflex, and narcosis) were seen predominatly at the highest exposure level. Mortality at the highest concentration was 100% in males compared to 82% for controls at 100 weeks. Absolute and relative liver and kidney weights were increased in males at the two highest levels and females at the highest level of exposure. An increase in incidence and severity of kidney lesions (mineralization, tubular dilation, glomerulosclerosis, interstitial nephritis/fibrosis, and transitional hyperplasia) were observed in both sexes at 2500 and 5000 ppm. Other lesions secondary to the kidney effects (soft tissue mineralization, parathyroid hyperplasia [females], myocardial degeneration, and fibrous osteodystrophy) were observed at 2500 and 5000 ppm. Basophilic cell foci of the liver, splenic hemosiderosis, rhinitis, and squamous metaplasia of the respiratory epithelia were also seen in both sexes at 5000 ppm.